REMARKS

Claims 1-7 and 10-13 are pending. Applicants have added new claim 14. Claims 1-7 and 10-14 will therefore pending upon entry of the proposed amendment.

New claim 14 is directed to formulations that are "substantially free of a co-solvent." Support for new claim 14 can be found throughout the specification, e.g., at page 2, lines 1-10.

Claims 1-7 and 11-12 remain rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over **"Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier Systems," Chem. Rev. 1998, 98, pp 2045, 2048 (Table 2); and 2063),** wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031" (Office Action, page 3, bold emphasis in original).

This is respectfully traversed.

[1] Claim 1 is directed to an HFA drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin.

[2] Muller

Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. There is no disclosure of acylated cyclodextrins. Rather, Muller focuses heavily on hydroxyalkyl modified cyclodextrins; see Muller at page 2, paragraph 0024:

> The cyclodextrine used according to the invention can be a native or modified α-, β-, or γ-cyclodextrine. Examples of modified cyclodextrines are hydroxymethyl-α-cyclodextrine, hydroxyethyl-α-cyclodextrine, hydroxypropyl-α-cyclodextrine, α-cyclodextrine butyl sulphonate, α-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine; hydroxymethyl β-cyclodextrine, hydroxyethyl-β-cyclodextrine, hydroxypropyl-β-cyclodextrine, β-cyclodextrine butyl sulphonate, β-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine as well as hydroxymethyl-γ-cyclodextrine, hydroxyethyl-γ-cyclodextrine, hydroxypropyl-γ-

> cyclodextrine, γ-cyclodextrine butyl sulphonate, γ-cyclodextrine butyl fluoride and sulphobutyl-γ-cyclodextrine.

In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations.

[3] Uekama

Uekama is a review article entitled "Cyclodextrin Drug Carrier Systems." Uekama describes cyclodextrin derivatives (including acylated cyclodextrins); however, Uekama does not refer at all to formulations that are to be delivered to the lung *via* an inhaled aerosol composition (*cf*: Muller discussion above).

Uekama discloses a table ("Table 1" in Uekama at page 2047) that includes "[t]ypical examples of the pharmaceutically useful β-cyclodextrin derivatives" (Uekama, page 2046). In Uekama's Table 1, the derivatives are "classified into hydrophilic, hydrophobic, and ionic derivatives" (Uekama, page 2046). "Hydroxyalkylated cyclodextrins," i.e., the type of cyclodextrin that is used in all of Muller's exemplified formulations, are classified by Uekama as "**hydrophilic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added). In contrast, "acylated cyclodextrins," which are required by the present claims, are classified by Uekama as "**hydrophobic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added).

[4] The Supreme Court discussed the requirements for making rejections under 35 U.S.C. 103 in *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007, bolded, underline emphasis added).

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the

> legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.
>
> When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, **a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, **it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**. This is so because **inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known**.

Thus, a claim is not proved obvious merely by showing that the elements of that claim can be found in the prior art. Rather, the Office must articulate some reason as to why a person of ordinary skill in the art, at the time of the invention, would have combined the elements in the manner required by the claim. It is respectfully submitted that one would not have combined Muller and Uekama for any one of the following independent reasons.

[5] Here, claim 1 is directed to an HFA (hydro fluoro alkane) drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin.

[A] As of Applicants' filing date, the use of cyclodextrins for the formulation of inhalation products in HFA's was rare (see specification at page 2, lines 1-2). According to the specification; "[u]se of cyclodextrins in HFA formulations is rare because most cyclodextrins, in particular natural cyclodextrins, are insoluble in HFAs" (see specification at page 2, lines 2-4).

The present claims require an acylated cyclodextrin, which according to Uekama, are **hydrophobic** in nature (see Tables 1 and 2 on pages 2047 and 2048 of Uekama). One advantage of the claimed formulations is that a storage stable formulation is achieved.

In contrast, Muller focuses heavily on hydroxyalkyl modified cyclodextrins, which according to Uekama, are **hydrophilic** in nature (acylated cyclodextrins are not disclosed in Muller). In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations. In addition, the Muller formulations include one and typically two co-solvents, such as ethanol. The co-solvent(s) appear to be used by Muller to solubilize the cyclodextrins. This aspect of Muller is discussed in the specification at page 2, lines 4-8):

> In WO03/066031, cyclodextrins are used to stabilize drug suspensions. This however is only possible by the addition of at least one co-solvent (one hydrophilic additive, such as PEG: poly ethylene glycol), but preferably two (one hydrophilic additive and ethanol). These co-solvents solubilize the cyclodextrins, and thus make them useful as stabilizers.

There is nothing in the prior art of record that would have led one to ignore outright Muller's clear preference for hydrophilic cyclodextrins (e.g., including a hydrophilic additive to accommodate the hydrophilic cyclodextrins) and turn to hydrophobic cyclodextrins, much less turn to the partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrins of the present claims. Accordingly, one would not have been motivated to combine Muller and Uekama in the manner proposed by the Office.

[B] Further, as explained in the specification, an HFA (hydro fluoro alkanes) or mixtures thereof, are used, e.g., as propellants in inhalation delivery devices (e.g., pressure metered dose inhalers).

Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. Further, Muller's disclosure relates solely to inhaled formulations, it does not concern any other type of formulation.

Uekama discloses formulations that can be administered orally, rectally, nasally, ocularly and dermally (see Uekama at pages 2056-9). When discussing nasal delivery, Uekama mentions 'water-soluble cyclodextrin complexes' (line 2 of the Nasal Delivery section on page 2057) and all the cyclodextrins discussed in this section of Uekama are **hydrophilic**. Thus, the skilled artisan is not taught about the inclusion of a hydrophobic cyclodextrin in a formulation for nasal delivery. The last sentence of the 'Nasal Delivery' section of Uekama mentions that the potential of cyclodextrins to improve the pulmonary delivery of drugs has been evaluated. As this is in the same paragraph and section of Uekama where only hydrophilic cyclodextrins have been discussed and exemplified, **the skilled artisan is again not taught about the inclusion of a hydrophobic cyclodextrin in a pulmonary formulation**.

The formulation of Muller is for administration to the respiratory tract (line 4 of [0004]), i.e., pulmonary delivery. Given what is disclosed in Uekama about this form of delivery, it is submitted that nothing in the prior art of record would have led one to combine the disclosure of Muller and Uekama in the manner suggested by the Office.

[C] Finally, the drug formulations of the present claims are useful for pulmonary or nasal delivery (see, e.g., page 2 lines 20-21 of the present application). There is nothing in the prior art of record, given in particular what is disclosed in Muller and Uekama about the above-mentioned forms of delivery, that would have led one to include a partially or fully acylated cyclodextrin (which are examples of hydrophilic cyclodextrins) in a formulation for pulmonary or nasal delivery. As such, there is nothing in the prior art of record that would have led one to combine the disclosure of Muller and Uekama in the manner suggested by the Office. Applicants respectfully request reconsideration and withdrawal of the rejection for this additional and independent reason.

[D] In summary, Applicants therefore respectfully request that the rejection of 1-7 and 11-12 be reconsidered and withdrawn because the Office, at most, has only identified the elements of the present claims in three unrelated disclosures, but has not articulated any reason

why the claimed kits and pharmaceutical compositions would have been obvious at the time that the present application was filed. Applicants also respectfully request that the rejection not be applied to new claim 14.

[6] Applicants submit that new claim 14 is patentable over the prior art of record for the following additional and independent reason.

[A] The Muller formulations, while containing a cyclodextrin (hydrophilic hydroxyalkylated cyclodextrins are exemplified in Muller, which are different from the hydrophobic acylated cyclodextrins of the present claims), also include one and typically two co-solvents, such as ethanol. The co-solvent(s) appear to be used by Muller to solubilize the cyclodextrins. This is discussed in the specification at page 2, lines 4-8):

> In WO03/066031, cyclodextrins are used to stabilize drug suspensions. This however is only possible by the addition of at least one co-solvent (one hydrophilic additive, such as PEG: poly ethylene glycol), but preferably two (one hydrophilic additive and ethanol). These co-solvents solubilize the cyclodextrins, and thus make them useful as stabilizers.

[B] Although the hydroxyalkylated cyclodextrins exemplified in Muller and the acylated cyclodextrins of the present claims are different – the former are hydrophilic while the latter are hydrophobic – the Office has argued that one would have combined Muller and Uekama because these two different types of cyclodextrins are both soluble in ethanol (see, in particular, the Office Action at the paragraph bridging pages 5 and 6 and page 7, second paragraph).

[C] The inventors, however, have discovered HFA (hydro fluoro alkane) drug formulations that **(i)** include a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin; and **(ii)** do **not** require any co-solvents. See specification at page 2, lines 9-10: "[t]he present invention has identified the correct cyclodextrins that do not require any co-solvents, and thus constitutes a major improvement to the invention of WO03/066031." New

claim 14, which is directed to formulations that are "substantially free of a co-solvent," embodies this feature.

[D] Thus, given the prior art available as of Applicants' filing date, the skilled person would not have been led to stabilize an HFA drug formulation with a cyclodextrin in the **absence** of a co-solvent, much less would have reasonably expected that such a formulation would have had the beneficial properties discovered by the present inventors. Thus, it is submitted that new claim 14 is patentable over the prior art of record for this additional and independent reason.

CONCLUDING FORMALITIES

Applicants submit that all claims are in condition for allowance.

The fee in the amount of $1,110 is being paid concurrently on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-0512US1 / 101287-1P US/R&I.

Respectfully submitted,

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